

## P. . . ENT COOPERATION TREA

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 25 March 1999 (25.03.99)	
<b>International application No.</b> PCT/US98/14289	<b>Applicant's or agent's file reference</b> CTLI-001/02WO
<b>International filing date</b> (day/month/year) 10 July 1998 (10.07.98)	<b>Priority date</b> (day/month/year) 10 July 1997 (10.07.97)
<b>Applicant</b> KÜNDIG, Thomas, M. et al	

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

09 February 1999 (09.02.99)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer</p> <p>Catherine Massetti</p> <p>Telephone No.: (41-22) 338.83.38</p>
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## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

MORAN, Tom, M.  
Cooley Godward LLP  
3000 El Camino Real  
Five Palo Alto Square  
Palo Alto, CA 94306-2155  
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year) 25 March 1999 (25.03.99)	<b>IMPORTANT NOTIFICATION</b>
Applicant's or agent's file reference CTLI-001/02WO	
International application No. PCT/US98/14289	International filing date (day/month/year) 10 July 1998 (10.07.98)

## 1. The following indications appeared on record concerning:

☒ the applicant      ☒ the inventor      ☐ the agent      ☐ the common representative

Name and Address SIMARD, John, J., L. Suite 1014 24 Wellesley Street, West Toronto, Ontario M4Y 1G1 Canada	State of Nationality **	State of Residence CA
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person      ☐ the name      ☒ the address      ☒ the nationality      ☒ the residence

Name and Address SIMARD, John, J., L. 11767 Seminole Circle Northridge CA 91326 United States of America	State of Nationality CA	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer  Catherine Massetti
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>CTLI-001/02W0</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 98/ 14289</b>	International filing date (day/month/year) <b>10/07/1998</b>	(Earliest) Priority Date (day/month/year) <b>10/07/1997</b>
Applicant <b>CTL IMMUNOTHERAPIES CORPORATION et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

## 4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

## 5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

## 6. The figure of the drawings to be published with the abstract is Figure No. .

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 98/14289

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K39/00 A61K38/19 A61K9/00 //(A61K39/00,38:19)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K -

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 17167 A (GFF) 29 June 1995 see the whole document	1,4-10, 17-19
Y	R. PETERS ET AL.: "Tryptophan and serotonin metabolism after sustained tryptophan infusion." NEUROCHEMISTRY INTERNATIONAL, vol. 6, no. 5, 1984, pages 685-692, XP002095831 see abstract --- -/--	1,4,7-9, 14-16, 22-24, 28,30-38



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

8 March 1999

Date of mailing of the international search report

29/03/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Nooij, F

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 98/14289

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	<p>S. OEHEN ET AL.: "Antivirally protective cytotoxic T cell memory to lymphocytic choriomeningitis virus is governed by persisting antigen."  THE JOURNAL OF EXPERIMENTAL MEDICINE,  vol. 176, no. 5, 1 November 1992, pages  1273-1281, XP002095832  New York, NY, USA  see abstract  see page 1278, left-hand column, line 33 -  line 36  see page 1279, right-hand column, line 18  - line 33</p>	<p>1,4,7-9,  14-16,  22-24,  28,30-38</p>
A	<p>---  M. OLDSTONE ET AL.: "Discriminated selection among viral peptides with the appropriate anchor residues: Implications for the size of the cytotoxic T-lymphocyte repertoire and control of viral infection."  JOURNAL OF VIROLOGY,  vol. 69, no. 12, December 1995, pages  7423-7429, XP002095833  Washington, DC, USA  see abstract</p>	<p>1-38</p>
A	<p>---  T. KÜNDIG ET AL.: "On the role of antigen in maintaining cytotoxic T-cell memory."  PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE U.S.A.,  vol. 93, no. 18, 3 September 1996, pages  9716-9723, XP002095834  Washington, DC, USA  see abstract</p>	<p>1-38</p>
A	<p>---  D. MOSKOPHIDIS ET AL.: "Immunobiology of cytotoxic T-cell escape mutants of lymphocytic choriomeningitis virus."  JOURNAL OF VIROLOGY,  vol. 69, no. 4, April 1995, pages  2187-2193, XP002095835  Washington, DC, USA  see abstract  see figure 1A</p> <p>---  -/--</p>	<p>1-38</p>

## INTERNATIONAL SEARCH REPORT

International Application No

CT/US 98/14289

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
P, X	<p>L. DURRANT: "Cancer vaccines." ANTI-CANCER DRUGS, vol. 8, no. 8, September 1997, pages 727-733, XP002095836 Oxford, GB see page 728, right-hand column, line 1 - line 36 see page 730, left-hand column, line 42 - right-hand column, line 8 see page 730, right-hand column, line 19 - line 40</p> <p>-----</p>	<p>1,4-6,9, 10,17-21</p>

### ation on patent family members

CT/US 98/14289

Form PCT/ISA/210 (patent family annex) (July 1992)

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/14289

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 1-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



## PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

**PCT**NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

(PCT Rule 44.1)

To:

COOLEY GODWARD LLP  
Attn. MORAN, T.  
Five Palo Alto Square  
3000 El Camino Real  
Palo Alto, CA 94306-2155  
UNITED STATES OF AMERICADate of mailing  
(day/month/year)

29/03/1999

Applicant's or agent's file reference

CTLI-001/02W0

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 98/ 14289

International filing date  
(day/month/year)

10/07/1998

Applicant

CTL IMMUNOTHERAPIES CORPORATION et al.

- 1.
- ☒
- The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.**Where?** Directly to the International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

- 2.
- ☐
- The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

- 3.
- ☐
- With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

- 4.
- Further action(s):**
- The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

CTLI-001/00CA  
CTLI-001/01US  
File IDS  
with EP  
Search Report  
29 APR 99  
25 JES

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patendaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
Fax: (+31-70) 340-3016

Authorized officer

Barbara Klaver

Article 19  
Amendment  
29 APR 99  
29 APR 9912 APR 99  
13 APR 99

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

**"Statement under article 19(1)" (Rule 48.4)**

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

**Consequence if a demand for international preliminary examination has already been filed**

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

**Consequence with regard to translation of the international application for entry into the national phase**

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

RECEIVED

DEC 27 1999

Group 3700

PATENT COOPERATION TREATY

PCT

REC'D 05 OCT 1999

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

09/380534

Applicant's or agent's file reference CTLI-001/02WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/14289	International filing date (day/month/year) 10 JULY 1998	Priority date (day/month/year) 10 JULY 1997
International Patent Classification (IPC) or national classification and IPC IPC(6): A161K 39/00, 38/19, 45/05; C07K 14/5354 and US Cl.: 424/277.1, 85.2		
Applicant CTL IMMUNOTHERAPIES CORPORATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ ~~Certain defects in the international application~~
- VIII ☐ Certain observations on the international application

Date of submission of the demand 02 FEBRUARY 1999	Date of completion of this report 11 SEPTEMBER 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX Martha Lubet Telephone No. (703) 308-0196

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/14289

## I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments):*

☒ the international application as originally filed.

☒ the description, pages (See Attached), as originally filed.

pages \_\_\_\_\_, filed with the demand.

pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

☒ the claims, Nos. (See Attached), as originally filed.

Nos. \_\_\_\_\_, as amended under Article 19.

Nos. \_\_\_\_\_, filed with the demand.

Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

☒ the drawings, sheets/fig (See Attached), as originally filed.

sheets/fig \_\_\_\_\_, filed with the demand.

sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of:

☒ the description, pages none.

☒ the claims, Nos. none.

☒ the drawings, sheets/fig none.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/14289

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>1-38</u>	YES
	Claims <u>none</u>	NO
Inventive Step (IS)	Claims <u>none</u>	YES
	Claims <u>1-38</u>	NO
Industrial Applicability (IA)	Claims <u>1-38</u>	YES
	Claims <u>none</u>	NO

**2. CITATIONS AND EXPLANATIONS**

Claims 1-38 lack an inventive step under PCT Article 33(3) as being obvious over Puccetti et al. or Grohmann et al. in view of Elliott et al. US 5,478,556, Shapland et al. US 5,286,254, Amkraut et al. US 4,439,199 and Mertelsmann et al. US 4,908,433.

Puccetti et al. teach intrasplenic immunization to elicit antigen specific CD8+ cell mediated by depositing a tumor or influenza virus antigen adsorbed onto a membrane in the splenic capsule (see page 1447, 1448 and 1449, in particular).

Puccetti et al. further teach that because soluble proteins are excluded from the class I-restricted pathway responses of antigen presentation in most cells, CD8+ T lymphocytes are not in general activated by cutaneous challenge with protein antigens (see page 1446, in particular).

Grohmann et al. teach that methods of immunizing with minute amounts of antigen include depositing the antigen into lymph node or spleen (see abstract, and page 9, in particular). Grohmann et al. further exemplify eliciting CTL responses to tumor antigens by intrasplenic immunization of tumor antigens bound to nitrocellulose (see page 10, in particular). Grohmann et al. teach immunization with multiple antigens (see page 12, in particular).

Puccetti et al. and Grohmann et al. do not teach a method of inducing a CTL response by administering the antigen via a device held external of the animal's body through a transmission line and catheter positioned to deliver the antigen containing composition to the lymph node or spleen.

However, Mertelsmann et al. disclose administering of cytokine, IL-2, via an osmotic infusion pump (see column 34, lines 41-67 and column 32, lines 14-29, in particular).

Shapland et al. teach a drug delivery device for delivering a (Continued on Supplemental Sheet.)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/14289

## Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Sheet 10

Continuation of: Boxes I - VIII

### I. BASIS OF REPORT:

THIS REPORT HAS BEEN DRAWN ON THE BASIS OF THE DESCRIPTION,  
PAGES, 1-65 AND SEQUENCE LISTINGS PAGES 1-119 AND 121, AS ORIGINALLY FILED.  
PAGES, NONE, FILED WITH THE DEMAND.

AND ADDITIONAL AMENDMENTS:

NONE

THIS REPORT HAS BEEN DRAWN ON THE BASIS OF THE CLAIMS,  
NUMBERS, 1-38, AS ORIGINALLY FILED.

NUMBERS, NONE, AS AMENDED UNDER ARTICLE 19.

NUMBERS, NONE, FILED WITH THE DEMAND.

AND ADDITIONAL AMENDMENTS:

NONE

THIS REPORT HAS BEEN DRAWN ON THE BASIS OF THE DRAWINGS,  
SHEETS, 1-6, AS ORIGINALLY FILED.

SHEETS, NONE, FILED WITH THE DEMAND.

AND ADDITIONAL AMENDMENTS:

NONE

### V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (CONTINUED):

DRUG LOCALLY TO A BODY TISSUE IN ORDER TO TREAT A LOCALIZED REGION OR TISSUE SUCH AS REGIONAL LYMPH NODE (SEE COLUMN 2, LINES 25-39, AND COLUMN 12, LINES 11-20, IN PARTICULAR). SHAPLAND ET AL. ALSO DISCLOSE THAT SUCH A DEVICE IS SUITABLE FOR ADMINISTRATION OF IMMUNOMODULATOR DRUGS (SEE COLUMN 11, LINES 19-25, IN PARTICULAR).

AMKRAUT ET AL. DISCLOSE THE ADMINISTRATION OF IMMUNOMODULATORS IN CONTROLLED AND CONTINUOUS DOSAGE FOR PRODUCING LOCAL AND SYSTEMIC RESPONSE. AMKRAUT ET AL. TEACH ADMINISTRATION OF IMMUNOMODULATORS BY SLOW ADMINISTRATION OF THE IMMUNOMODULATOR VIA EXTERNAL SYSTEMS CARRIED BY THE HOST THROUGH A CATHETER OR NEEDLE (SEE COLUMN 3, LINE 25 THROUGH COLUMN 6, LINE 34, IN PARTICULAR).

THEREFORE IT WOULD HAVE BEEN OBVIOUS TO ONE WITH SKILL IN THE ART AT THE TIME OF THE INVENTION TO MODIFY THE METHODS OF INDUCING IMMUNE RESPONSES TO ANTIGENS TAUGHT BY PUCETTI ET AL. OR GROHMANN ET AL. BY ADMINISTERING ANYGENS VIA OSMOTIC PUMPS OR DEVICES TAUGHT BY THE MERTELSMANN ET AL. OR SHAPLAND ET AL. AMKRAUT ET AL. OR ANY OF THE PUMPS DISCLOSED IN THE INSTANT APPLICATION (SEE PAGE 56, IN PARTICULAR).

GROHMANN ET AL. AND PUCETTI ET AL. DO NOT TEACH THE ADMINISTRATION OF COMPOSITION COMPRISING AN ANTIGEN AND A CYTOKINE CAPABLE OF ENHANCING A CTL RESPONSE. HOWEVER, ELLIOTT ET AL. TEACH A METHOD OF INDUCING AN IMMUNE RESPONSE BY ADMINISTERING A TUMOR ANTIGEN COMPRISING A MIXTURE OF TUMOR ASSOCIATED ANTIGENS WITH LOW DOSES OF IL-2 AND G-CS (SEE COLUMN 2, LINES 31-57 AND CLAIMS 1-3, IN PARTICULAR).

THEREFORE IT WOULD HAVE BEEN OBVIOUS TO ONE WITH SKILL IN THE ART AT THE TIME OF THE INVENTION TO MODIFY THE METHODS OF INDUCING IMMUNE RESPONSE TO ANTIGENS TAUGHT GROHMANN ET AL., PUCETTI AL., MERTELSMANN ET AL., OR SHAPLAND ET AL. AND AMKRAUT ET AL. BY CO-ADMINISTERING CYTOKINES SUCH AS THE ONES USED BY ELLIOTT ET AL. WITH THE EXPECTATION THAT THE CYTOKINES WOULD ENHANCE THE IMMUNE RESPONSE TO THE ANTIGENS.

### NEW CITATIONS

PUCETTI ET AL. USE OF A SKIN TEST ASSAY TO DETERMINE TUMOR SPECIFIC CD8+ T CELL REACTIVITY. EUR. J. IMMUNOLOGY. 1994. VOL. 24, PAGES 1146-1452, SEE ENTIRE ARTICLE.

GROHMANN ET AL. INTRASPLENIC IMMUNIZATION FOR THE INDUCTION OF HUMORAL AND CELL-MEDIATED IMMUNITY TO NITROCELLOULOSE-BOUND ANTIGEN. J. OF IMMUNOLOGICAL METHODS. 1991. VOL. 137. PAGES 9-16, SEE ENTIRE ARTICLE.

US 5,478,556 (ELLIOTT ET AL.) 26 DECEMBER 1995, SEE ENTIRE DOCUMENT.

US 4,439,199 (AMKRAUT ET AL) 27 MAY 1984, SEE ENTIRE DOCUMENT.

US 5,286,254 (SHAPLAND ET AL.) 15 FEBRUARY 1994, SEE ENTIRE DOCUMENT.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/14289

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 11

US 4,908,433 (MERTELSMANN ET AL.) 13 MARCH 1990, SEE ENTIRE DOCUMENT.



## PATENT COOPERATION TREATY

PCT

REC'D 09 NOV 1999

WIPO

PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CTLI-001/02WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/14289	International filing date (day/month/year) 10 JULY 1998	Priority date (day/month/year) 10 JULY 1997
International Patent Classification (IPC) or national classification and IPC IPC(6): A161K 39/00, 38/19, 45/05; C07K 14/5354 and US Cl.: 424/277.1, 85.2		
Applicant CTL IMMUNOTHERAPIES CORPORATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

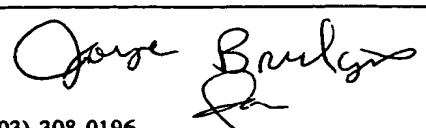
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

CORRECTED  
VERSION

Date of submission of the demand 09 FEBRUARY 1999	Date of completion of this report 11 SEPTEMBER 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer Martha Lubet 
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/14289

## I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments):*

☒ the international application as originally filed.

☒ the description, pages (See Attached), as originally filed.

pages \_\_\_\_\_, filed with the demand.

pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

☒ the claims, Nos. (See Attached), as originally filed.

Nos. \_\_\_\_\_, as amended under Article 19.

Nos. \_\_\_\_\_, filed with the demand.

Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

☒ the drawings, sheets/fig (See Attached), as originally filed.

sheets/fig \_\_\_\_\_, filed with the demand.

sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of:

☒ the description, pages none.

☒ the claims, Nos. none.

☒ the drawings, sheets/fig none.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/14289

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>1-38</u>	YES
	Claims <u>none</u>	NO
Inventive Step (IS)	Claims <u>none</u>	YES
	Claims <u>1-38</u>	NO
Industrial Applicability (IA)	Claims <u>1-38</u>	YES
	Claims <u>none</u>	NO

**2. CITATIONS AND EXPLANATIONS**

Claims 1-38 lack an inventive step under PCT Article 33(3) as being obvious over Puccetti et al. or Grohmann et al. in view of Elliott et al. (US 5,478,556), Shapland et al. (US 5,286,254), Amkraut et al. (US 4,439,199) and Mertelsmann et al. (US 4,908,433).

Puccetti et al. teach intrasplenic immunization to elicit antigen specific CD8+ cell mediated by depositing a tumor or influenza virus antigen adsorbed onto a membrane in the splenic capsule (see page 1447, 1448 and 1449, in particular).

Puccetti et al. further teach that because soluble proteins are excluded from the class I-restricted pathway responses of antigen presentation in most cells, CD8+ T lymphocytes are not in general activated by cutaneous challenge with protein antigens (see page 1446, in particular).

Grohmann et al. teach that methods of immunizing with minute amounts of antigen include depositing the antigen into lymph node or spleen (see abstract, and page 9, in particular). Grohmann et al. further exemplify eliciting CTL responses to tumor antigens by intrasplenic immunization of tumor antigens bound to nitrocellulose (see page 10, in particular). Grohmann et al. teach immunization with multiple antigens (see page 12, in particular).

Puccetti et al. and Grohmann et al. do not teach a method of inducing a CTL response by administering the antigen via a device held external of the animal's body through a transmission line and catheter positioned to deliver the antigen containing composition to the lymph node or spleen.

However, Mertelsmann et al. disclose administering of cytokine, IL-2, via an osmotic infusion pump (see column 34, lines 41-67 and column 32, lines 14-29, in particular).

~~Shapland et al. teach a drug delivery device for delivering a drug locally to a body tissue in order to treat a localized~~ (Continued on Supplemental Sheet.)

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

**I. BASIS OF REPORT:**

This report has been drawn on the basis of the description, pages, 1-65 and sequence listings pages 1-119 and 121, as originally filed. pages, NONE, filed with the demand. and additional amendments: NONE

This report has been drawn on the basis of the claims, numbers, 1-38, as originally filed. numbers, NONE, as amended under Article 19. numbers, NONE, filed with the demand. and additional amendments: NONE

This report has been drawn on the basis of the drawings, sheets, 1-6, as originally filed. sheets, NONE, filed with the demand. and additional amendments: NONE

**V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):**

region or tissue such as regional lymph node ( see column 2, lines 25-39, and column 12, lines 11-20, in particular). Shapland et al. also disclose that such a device is suitable for administration of immunomodulator drugs ( see column 11, lines 19-25, in particular).

Amkraut et al. disclose the administration of immunomodulators in controlled and continuous dosage for producing local and systemic response. Amkraut et al. teach administration of immunomodulators by slow administration of the immunomodulator via external systems carried by the host through a catheter or needle( see column 3, line 25 through column 6, line 34, in particular).

Therefore it would have been obvious to one with skill in the art at the time of the invention to modify the methods of inducing immune responses to antigens taught by Puccetti et al. or Grohmann et al. by administering antigens via osmotic pumps or devices taught by the Mertelsmann et al. or Shapland et al. Amkraut et al. or any of the pumps disclosed in the instant application ( see page 56, in particular).

Grohmann et al. and Puccetti et al. do not teach the administration of composition comprising an antigen and a cytokine capable of enhancing a CTL response. However, Elliott et al. teach a method of inducing an immune response by administering a tumor antigen comprising a mixture of tumor associated antigens with low doses of IL-2 and G-CS ( see column 2, lines 31-57 and claims 1-3, in particular).

Therefore it would have been obvious to one with skill in the art at the time of the invention to modify the methods of inducing immune response to antigens taught Grohmann et al., Puccetti al., Mertelsmann et al., or Shapland et al. and Amkraut et al. by co-administering cytokines such as the ones used by Elliott et al. with the expectation that the cytokines would enhance the immune response to the antigens.

Applicant's response to the written opinion in the communication filed 23 August 1999 has been considered but is not persuasive. Applicant's argument that the Grohmann et al. teaches away from the claimed invention because Grohmann et al. immunizes via the intrasplenic route by implanting a nitrocellulose filter which contains antigen is not persuasive. Grohmann et al. clearly teaches intrasplenic immunization by administering antigen to spleen. Applicant's response that Grohmann et al. teaches away from the claimed invention because Table 2 shows very poor T cell response is not persuasive since Table 2 teaches a strong T cell response in animals immunized with 80 kDa antigen. Similarly Table 1 teaches that intrasplenic immunization of mice induces CTL response to 80kDa antigen.

Applicant's response that Puccetti et al. does not teach a method for inducing CD8+ T cell by intrasplenic immunization since the purpose was to establish a method of detecting CD8+ T lymphocytes. This argument is not persuasive since the methods of immunization taught by Puccetti et al. are intrasplenic immunization.

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 11

Applicant' argues that one with skill in the art would not have been motivated to modify the immunization protocol of Puccetti or Grohmann et al. by administering the antigen via osmotic pump instead of implanting the antigen bound to a solid phase.

However, the secondary references teach administration of substance, including immunomodulators, via an external device.

Applicant's response that one with skill could not use the device taught by Shapland, Amkraut or Mertelsmann to deliver antigen bound to solid phase is not persuasive. Applicant's further argues that the methods of Grohmann et al. and Puccetti et al. would not be expected to induce CTL responses is not persuasive since Grohmann et al. clearly show that intrasplenic immunization is effective in eliciting CTL responses. Therefore the invention as a whole is prima facie obvious in view of the teachings of the cited prior art.

## ----- NEW CITATIONS -----

PUCETTI et al. Use Of A Skin Test Assay To Determine Tumor Specific CD8+ T Cell Reactivity. Eur. J. Immunology. 1994. Vol. 24, pages 1146-1452, see entire article.

GROHMANN et al. Intrasplenic Immunization For The Induction Of Humoral And Cell-Mediated Immunity To Nitrocellulose-Bound Antigen. J. of Immunological Methods. 1991. Vol. 137. pages 9-16, see entire article.

US 5,478,556 (ELLIOTT et al.) 26 December 1995, see entire document.

US 4,439,199 (AMKRAUT et al) 27 May 1984, see entire document.

US 5,286,254 (SHAPLAND et al.) 15 February 1994, see entire document.

US 4,908,433 (MERTELSMANN et al.) 13 March 1990, see entire document.